REMARKS

Claims 1-39, as amended, appear in this application for the Examiner's review and consideration. Claims 18-38 are currently withdrawn but will be rejoined when claim 1 is allowed. Claim 16 has been cancelled and its content has been incorporated into the related claims as described below. Claims 1, 3, 4, 6, 7, 11, 13, and 17 have been amended. Claims 1-15, 17 and 39 are presently pending for examination. Claim 1 has been amended to include a radioisotope which was previously recited in the currently cancelled claim 16. Claims 4, 6, 7, 11 and 13 have been rewritten as independent claims and have been amended to include a radioisotope which was previously recited in the currently cancelled claim 16. Claim 17 has been amended to depend from claim 1, instead of the currently cancelled claim 16. Claim 3 has been amended to depend on a preceding claim (claim 1) instead of a later claim (claim 4). The amended claims are supported by the specification and original claims so that their entry at this time is warranted. No new matter is being introduced.

Claims 1-17 were rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,051,554 to Hornik *et al.* (referred to hereafter as "Hornik"). Hornik discloses backbone cyclized somatostatin analogs as well as methods to synthesize and use those analogs for pharmaceutical applications. Although both the application and Hornik disclose backbone cyclized somatostatin analogs, they are different in at least two aspects. First, in the application the backbone cyclized somatostatin analogs are comprised of a chelating moiety or a chelating moiety complexed with a radioisotope, which is not disclosed in Hornik. As explained in paragraph [0031] of the published application, the attachment of a chelating moiety or a chelating moiety complexed with a radioisotope to backbone cyclized analogs according to the invention maintains or increases the favorable properties of these analogs. Second, none of the specific analogs disclosed in claims 1-15 and 17 are present in Hornik. Since different somatostatin analogs have different receptor affinities and therapeutic applications, the somatostatin analogs in the application are distinct from those of Hornik.

In order for a prior art reference to anticipate a claimed invention, the reference must teach every aspect of the claimed invention. Hornik fails to teach each and every step of Applicants' invention and therefore it cannot anticipate the invention as presently claimed. In view of the foregoing, Applicants request that the anticipation rejection based on Hornik be withdrawn.

Claim 39 was rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,871,711 to Dean *et al.* (referred to hereafter as "Dean"). The Examiner is correct in pointing out that Dean teaches radioactively labeled somatostatin derived peptides for imaging sites in a mammalian body. But these somatostatin analogs do not have cyclized backbone as disclosed in the application. With the extra stability conferred by backbone cyclization, the Applicant's invention makes it possible to produce lower molecular weight analogs which have superior properties in terms of tissue permeability. Low level tissue permeability of somatostatin analogs has been a major obstacle to their in vivo application either as diagnostic or therapeutic reagents. Thus the differences in the backbone structure of the somatostatin analogs in the application and the reference are significant.

In order for a prior art reference to anticipate a claimed invention, the reference must teach every aspect of the claimed invention. Dean fails to teach each and every step of Applicants' invention and therefore it cannot anticipate the invention as presently claimed. In view of the foregoing, Applicants respectfully request that the anticipation rejection based on Dean be withdrawn.

Claims 1-17 and 39 were also rejected under 35U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,051,554 to Hornik *et al.* (refered to hereafter as "Hornik") in view of U.S. Patent No. 5,871,711 to Dean *et al.* (referred to hereafter as "Dean"). Although Hornik does disclose backbone cyclized somatostatin analogs, it neither teaches nor suggests the production of the specific somatostatin analogs disclosed in the present application. As explained in paragraphs [0033] and [0349] of the published application, Applicants are the first to provide a panel of backbone cyclized radiolabeled somatostatin analogs having specific receptor selectivity for "customized" diagnosis and therapy of various cancers. Highly relevant to their diagnostic and therapeutic applications, the molecules of the present invention are advantageous over the cyclized somatostatin homologs disclosed in Dean. First, the somatostatin analogs according to the application are backbone cyclized peptides comprising at least one bridging group attached to the alpha nitrogen of alpha amino acid [0032] to form a covalent non-disulfide linkage, in contrast to the thioether linkage of Dean. Such linkage has advantages of inducing conformationally constraint to the peptides yielding increased activity and selectivity over Dean. Thus the molecules in the present invention are more stable than those of Dean. Second, the bicyclic analogs of the present invention that contain both covalent and

disulfide linkages confer a high degree of conformational rigidity to the peptide, and can act to enhance the binding of the peptide to its biological target (i.e., the somatostatin receptor). Again, such property is lacking in the somatostatin analogs of Dean.

Moreover, the backbone cyclized somatostatin analogs disclosed in the application are comprised of a chelating moiety or a chelating moiety complexed with a radioisotope, which is neither disclosed nor suggested in Hornik.

It was Applicants' present disclosure that taught the need and value of backbone cyclized somatostatin analogs with cyclic covalent linkage as well as a chelating moiety with or without a radioisotope. The Examiner's conclusion of obviousness therefore appears to be based on improper hindsight reasons. The Federal Circuit has expressly prohibited the use of hindsight as a substitute for the requirement that the references provide a motivation to make such alterations.

While the presently claimed invention may seem obvious to the Examiner now, in light of Applicants' disclosure, at the time the invention was made there was no teaching or suggestion by either Hornik or Dean, or any other reference, of the presently claimed molecules. Without some teaching or suggestion in the prior art of the need to modify molecules in Hornik or Dean, one skilled in the art would also not be motivated to modify the molecules disclosed in Hornik and Dean as suggested by the Examiner. To modify the molecules in Hornik and Dean as suggested by the Examiner, it would incurring additional cost and time to test the different structures and functions of the somatostatin analogs.

Most importantly, even there is an attempt to attach a radioisotope to the somatostatin analogs of Hornik, as might be motivated by Dean, it will not be successful. The attachment of a chelating moiety to a relatively short peptide, such as the somatostatin analogs, is not obvious and not straightforward since the chelating moiety is relatively large and its attachment usually interferes with the peptide's binding to the receptor due to masking and conformation change. In addition, conversion of a given active peptide to a radiolabeled analog is not straightforward since sequence adaptation should be made in order to retain binding and to enable labeling, as demonstrated in example 8. As explained in Dean (lines 54-57 of column 10 of the patent), to form a complex between a radioisotope and a radiolabel binding moiety of a somatostatin analog, it is essential to introduce a reducing agent which will break down the disulfide linkage present in the cyclized backbone of the bi-cyclic somatostatin analogs of Hornik. And there is no teaching or suggestion in

either reference regarding how to achieve the radiolabeled backbone cyclized somatostatin analogs disclosed in the application.

In order to make a proper obviousness rejection, there must first be some suggestion or motivation to modify the reference. Second, there must be some reasonable expectation of success in the prior art and it must "not based on applicant's disclosure." And finally, the prior art reference (or references when combined) must teach or suggest all claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). As Hornik and Dean fail to teach or suggest all of the somatostatin analogs of the presently claimed invention and further fail to provide any suggestion or motivation to modify the molecules disclosed in Hornik and Dean in the way suggested by the Examiner, Hornik and Dean cannot make obvious the presently claimed invention. Thus, Applicants respectfully request that this obviousness rejection be withdrawn.

In view of the above, it is respectfully submitted that all current rejections have been overcome and should be withdrawn. Accordingly, the entire application is believed to be in condition for allowance, early notice of which would be appreciated. Should the Examiner not agree, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of this application.

Respectfully submitted,

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